Remarks

Claims 21-36 are currently pending. Claims 22-28 and 30-36 stand rejected under 35 U.S.C. §112, first paragraph. Claims 21-36 stand rejected under 35 U.S.C. §103(a).

Applicants have amended the claims to place the application in condition for allowance. Claims 21, 22, 25-27, 29, 30, and 33-35 have been amended, claims 23, 24, 31, and 32 have been cancelled, and new claims 37 and 38 have been added. Support for the amendments is found throughout the specification. In particular, support for the amendments to claims 21 and 29 is found at page 8, line 30 to page 9, line 15 of the specification. Support for the amendments to claims 22 and 30 is found at page 9, lines 5-7 of the specification. Support for the amendments to claims 25, 27, 33, and 35 is found at page 8, lines 19-22 of the specification. Support for new claims 37 and 38 is found at page 9, lines 10-12 of the specification. Applicants submit that the amendments add no new matter.

Rejection of Claims 22-28 and 30-36 under 35 U.S.C. § 112, First Paragraph

Claims 22-25, 27, 30-33 and 35 stand rejected as failing to comply with the written description requirement under 35 U.S.C. §112, first paragraph for recitation of dose ranges not supported by the specification as originally filed. Claims 26-28 and 34-36 stand rejected for failing to comply with the enablement requirement under 35 U.S.C. §112, first paragraph for requiring achievement of recombinant human activated protein C (aPC) plasma level.

In response to this rejection, Applicants have amended claims 22 and 30 to specify dosages of about 5 μg/kg/hr to about 30 μg/kg/hr, as supported at page 9, lines 5-7 of the specification. Claims 25, 27, 33, and 35 have been amended to specify administration of activated protein C for about 1 to about 240 hours, as supported at page 8, lines 19-22 of the specification. Claims 23, 24, 31, and 32 have been cancelled, thereby obviating their rejection.

Applicants gratefully acknowledge the Examiner's suggestion for overcoming the rejection of claims 26-28 and 34-36 and have accordingly deleted the term "recombinant" with respect to an achieved aPC plasma level.

In view of the claim amendments, Applicants respectfully request withdrawal of the rejections of claims 22, 25-28, 30, and 34-36 under 35 U.S.C. §112, first paragraph.

Rejection of Claims 21-28 under 35 U.S.C. § 103(a)

Claims 21-28 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Glas-Greenwalt *et al.*, J. Lab. Clin. Med. (1986) 108:415-422 (Glas-Greenwalt *et al.*), Gruber *et al.*, Circulation (1990) 82:578-585 (Gruber *et al.*), and Foster *et al.*, U.S. Patent No. 5,516,650 (Foster *et al.*). Applicants respectfully traverse this rejection as applied to amended claims 21, 22, and 25-28. The Examiner has concluded it would have been obvious to one of ordinary skill in the art to develop a method of treatment for TTP using recombinant human PC in view of the references, as Glas-Greenwalt *et al.* teaches that patients with TTP have a protein C deficiency which can be normalized by plasma exchange, Gruber *et al.* teaches use of aPC as an antithrombotic agent in a baboon model of arterial thrombosis, and Foster *et al.* teaches recombinant production of protein C. Applicants respectfully assert that the Examiner has failed to set forth a *prima facie* case of obviousness and request withdrawal of this rejection.

In *Graham v. John Deere Co.*, 383 U.S. 1 (1966), the court defined the test for determining obviousness under 35 U.S.C. § 103: 1) determine the scope and content of the prior art; 2) ascertain the differences between the prior art and the claims at issue; 3) resolve the level of ordinary skill in the pertinent art; and 4) evaluate evidence of secondary considerations. The USPTO bears the burden of establishing a *prima facie* case. (*In re Piasecki*, 745 F.2d 1468 (Fed. Cir. 1984)). To establish a *prima facie* case, the Examiner must show 1) some suggestion or motivation to modify the reference or to combine reference teachings (*In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988)); 2) the proposed modification had a reasonable expectation of success by a skilled artisan at the time of the invention (*Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed. Cir. 1991)); and 3) the prior art reference or combination of references must teach or suggest all the claim limitations (see M.P.E.P. §§ 2142-2143; *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)). Applicants respectfully assert that the Examiner has not met the burden of establishing a *prima facie* case of obviousness.

The Examiner has concluded that the present invention is obvious upon review of all three references as a whole, without providing any evidence that the skilled artisan would have been motivated to combine and/or modify the cited prior art references to develop a method of treatment for TTP using recombinant human aPC. Applicants respectfully submit that neither the teachings of the prior art, the nature of the problem to be solved, nor the knowledge of one skilled in the art provides motivation to combine the references. As the Examiner has acknowledged, Glas-Greenwalt *et al.* does not teach recombinant human protein C, let alone recombinant human aPC or its use in treating TTP, and thus provides no motivation to combine with Gruber *et al.* and Foster *et al.*, which collectively are concerned with recombinant protein C and aPC.

Moreover, Glas-Greenwalt *et al.* examines levels of protein C without examination or discussion of levels of aPC, while Gruber *et al.* examines aPC without examination or discussion of levels of protein C. As is well known in the art, aPC and the inactive zymogen protein C are distinct molecules that differ both pharmacokinetically and pharmacodynamically (see Yan and Fisher, Shock (1999) vol. 12, 243, Exhibit A). Glas-Greenwalt *et al.* discloses protein C levels without any discussion of aPC or knowledge of whether the microvasculature of patients with TTP can support the conversion of protein C to aPC, which is central to treatment strategy with protein C or aPC (see second sentence, right column of abstract, page S69 of Yan and Dhainaut, Crit. Care. Med. (2001) 29, S69-S74, Exhibit B). Applicants acknowledge that plasma exchange as used in Glas-Greenwalt *et al.* may provide some amount of aPC as well as protein C. However, the circulating concentration of protein C in healthy adults is approximately 4000 to 5000 ng/mL, while the circulating level of aPC is approximately 1 to 3 ng/mL (see 2nd paragraph, right column, p. S70 of Yan and Dhainaut, Crit. Care. Med. (2001) 29, S69-S74, Exhibit B). Even if plasma exchange were to restore normal levels of circulating aPC, these amounts would be approximately 133- to 2000-fold less than the circulating levels of rAPC observed in Gruber *et al.* (see second paragraph, right column of Gruber *et al.*, wherein levels of approximately 0.40 mg/L (μg/mL, low dose) and 2.0 mg/L (μg/mL, high dose) rAPC were observed). Thus, Glas-Greenwalt *et al.* and Gruber *et al.* do not explicitly or implicitly provide motivation to combine, nor would one of skill in

the art be motivated to combine these references which respectively concern plasma levels of protein C and inhibition of thrombin formation by recombinant aPC.

Glas-Greenwalt *et al.* teaches that TTP is characterized by widespread occluding and persistent microthrombotic lesions, that a defective fibrin-clearing system would not be able to counteract the events after excessive platelet aggregation, and that partial reversal of the fibrinolytic abnormalities occurred in patients treated with daily, consecutive plasma exchanges. Glas-Greenwalt *et al.* thus indicates that beneficial treatment of TTP will include fibrinolytic activity. However, as detailed below, Gruber *et al.* summarizes that infusion of APC failed to demonstrate induction of fibrinolysis. One of skill in the art would therefore not be motivated to combine Glas-Greenwalt *et al.* and Gruber *et al.* from the aspect of the therapeutic need for fibrinolytic activity in treatment of TTP.

Foster *et al.* teaches availability of recombinant protein C and recombinant aPC along with the motivation to use a recombinant product. While generally disclosing applicability of human protein C and human aPC in the treatment of thrombotic disorders, Foster *et al.* does not disclose or suggest use of human protein C and human aPC in the treatment of TTP. The Examiner concludes that one would be motivated to combine Glas-Greenwalt *et al.* with Gruber *et al.* and Foster *et al.*, since Gruber *et al.* and Foster *et al.* provide motivation to develop and use PC as an antithrombotic agent to treat septic shock and stroke (which the Examiner asserts are final manifestations of TTP without providing any supporting evidence). While Gruber et al. and Foster *et al.* suggest use of PC or aPC as an antithrombotic agent, Foster *et al.* indicates use of aPC to prevent the coagulopathic effects of septicemia (i.e., use of aPC as an anticoagulant, not for its profibrinolytic properties). Neither reference makes any suggestion of use of PC or aPC for stroke. None of the 12 patients examined for levels of protein C (with no examination of aPC) by Glas-Greenwalt *et al.* were indicated for septic shock or stroke. One of skill in the art would therefore not have been motivated to combine the teachings of Glas-Greenwalt *et al.* with those of Gruber *et al.* and Foster *et al.* to treat TTP, based the teachings of Gruber *et al.* and Foster *et al.* that aPC is an antithrombotic agent that may be used to treat septicemia. Further evidence of the distinction between sepsis, stroke, and TTP is evident in a study published after the Applicants' priority date, in which 126 patients were treated for TTP or HUS with plasma exchange. Of those 126 patients, 2

were stated to have sepsis as a comorbid condition, not as a manifestation of TTP or HUS, while there was no mention of stroke (see Table 2, page 575 of Lara *et al.*, American J. of Med. (1999), 107:573-579 , Exhibit C).

Thus, Foster *et al.* does not motivate one of skill in the art to combine Foster *et al.* with Glas-Greenwalt *et al.* and Gruber *et al.*, Foster et al. and Gruber *et al.* with Glas-Greenwalt *et al.*, or Glas-Greenwalt *et al.* with Gruber *et al.* to treat TTP with recombinant human aPC. For the above reasons, Applicants respectfully submit that there is no motivation to combine the cited references in the references themselves, through the nature of the problem to be solved, or from the knowledge of one of skill in the art to develop a method of treatment for TTP using recombinant human aPC.

In addition to the lack of motivation to combine the cited prior art, combination of the references fails to provide a reasonable expectation of success. The Examiner has concluded that one skilled in the art would have had a reasonable expectation of success since Glas-Greenwalt *et al.* teach low levels of PC antigen in TTP patients, that plasma exchange resulted in temporary reversal of TTP abnormalities, and that Gruber *et al.* teach aPC inhibition of thrombus formation in a model of arterial thrombosis. While Glas-Greenwalt *et al.* teaches that patients with TTP have a protein C deficiency which can be normalized by plasma exchange, Glas-Greenwalt *et al.* does so with a very limited number of 4 patients. More particularly, Glas-Greenwalt *et al.* teaches that protein C antigen levels were measured in 6 patients, and that the values were low in three, borderline in one, and within the normal range in two (see second paragraph, right column, p. 419 and second paragraph, left column, p. 420). Glas-Greenwalt *et al.* thereby discloses that half, and at most, two-thirds of the patients examined had abnormally low levels of protein C. Accordingly, at least one-third, and possibly one-half of the 6 patients with TTP who were examined for protein C and treated by plasma exchange had <u>acceptable</u> levels of protein C prior to plasma exchange.

While Glas-Greenwalt *et al.* teaches that fibrinolytic abnormalities were accompanied by extremely low levels of protein C in three and a borderline low level in one of the six patients observed, Glas-Greenwalt *et al.* does not teach or suggest that protein C alone may be of therapeutic value in treating TTP, let alone teach or suggest use of activated protein C. Plasma exchange will clearly provide numerous blood components and factors in addition to the protein C, inhibitor of plasminogen

activator, and tissue plasminogen activator factors examined by Glas-Greenwalt *et al.* On the basis of plasma exchange, one of skill in the art would not be able to determine whether protein C was itself therapeutic or rather a surrogate marker of beneficial therapy provided in combination with or by other blood factors or components. Glas-Greenwalt *et al.* even states in the paragraph at page 421 "Whether repeated, although temporary, reversal of fibrinolytic and protein C abnormalities by plasma exchange contributes to the beneficial effects of this treatment, . . . , remain speculative." (emphasis added). In view of this speculation, the failure of Glas-Greenwalt *et al.* to suggest therapeutic benefit of protein C alone, the fact that plasma exchange provides numerous blood components in addition to protein C, and the fact that at least one-third of examined patients with TTP had normal levels of protein C, one of skill in the art would not have had a reasonable expectation of success in treating TTP with protein C, let alone aPC, based on the teachings of Glas-Greenwalt *et al.*

The teachings of Gruber *et al.* also do not provide a reasonable expectation of success in treating TTP with aPC, taken either in combination with Glas-Greenwalt *et al.* or alone. As noted above, Glas-Greenwalt *et al.* only examined levels of protein C, while Gruber *et al.* only examined aPC. While the plasma exchange utilized by Glas-Greenwalt *et al.* may have provided some level of aPC, it would have been minimal and, at best, achieved normal plasma levels of 1-3 ng/mL. These levels range from approximately 133 to 2000-fold less than the plasma levels observed by Gruber *et al.* during aPC infusion at the aPC doses taught therein. Furthermore, as noted above, Glas-Greenwalt *et al.* indicates that beneficial treatment of TTP will include fibrinolytic activity. In the specification, Applicants have taught that protein C, with its anticoagulant and profibrinolytic activities, along with its ability to inactivate PAI-1, is useful for the treatment of the occlusion of arterioles and capillaries by microthrombi that occur in patients with TTP and HUS (see p. 4, lines 7-11 and p. 7, lines 22-26). While Gruber *et al.* teaches that recombinant aPC, like plasma-derived aPC, possesses anticoagulant properties as demonstrated by inhibition of thrombus formation, Gruber *et al.* failed to demonstrate induction of fibrinolysis as a result of aPC infusion. Gruber *et al.* therefore fails to teach a key property of aPC that is beneficial in treating arterioles and capillaries that are occluded by microthrombi.

More specifically, Gruber *et al.* summarizes in the 4th paragraph, left column, page 584, "However, clot lysis in vitro was not increased in the absence of exogenous t-PA, and the D-dimer levels during infusion of both plasma derived APC and rAPC did not increase, failing to demonstrate induction of fibrinolysis as a result of aPC infusion." Gruber *et al.* proceeds to note "Thus, the suggested in vivo prothrombolytic effect of APC, which has been based on in vitro or ex vivo studies, remains unproven." (emphasis added). Gruber *et al.* further concludes in the paragraph in the right column, page 584 that "infused rAPC is a candidate for immediate and transient inhibition of arterial thrombotic events, for example, clot formation during cardiac surgery or rethrombosis after thrombolytic therapy, . . ." (emphasis added). Gruber *et al.* therefore teaches that aPC is a useful candidate for prevention and inhibition of thrombosis, but that its suggested profibrinolytic activity remains unproven. Gruber *et al.* thus does not support the profibrinolytic property of aPC which is useful in treating TTP, where microthrombi that occlude arterioles and capillaries are already formed. One of skill in the art would therefore not have had a reasonable expectation in treating TTP in view of Gruber *et al.* in combination with Glas-Greenwalt *et al.*

The combination of Glas-Greenwalt *et al.*, Gruber *et al.*, and Foster *et al.* fails to fulfill the third requirement in establishing a *prima facie* case, as these combined references fail to teach or suggest all the claim limitations. In particular, the references fail to teach the claimed dosage ranges, continuous infusion range, and achieved level of plasma aPC. The Examiner acknowledges that the dosages used in Gruber *et al.* are not the same as those claimed, but states that it was within the skill of the ordinary artisan to determine human dosages based on the baboon model, and that it is not inventive to discover the optimum or workable ranges by routine experimentation. Applicants have not, however, merely discovered an optimum or workable range by routine experimentation. Rather, Applicants have discovered a critical dosage range and a critical duration and mode of continuous infusion, since higher dosages create risks of bleeding which could cause serious adverse events or lethality in humans.

In particular, Gruber *et al.* teach high dosages of 250 µg/kg/hr and 1000 µg/kg/hr, whereas the present invention claims low dosages of 1 µg/kg/hr to 50 µg/kg/hr, and more preferably about 5 µg/kg/hr to about 30 µg/kg/hr. The dosages

taught by Gruber *et al.* are therefore 5- and 20-fold higher than the highest dose of the present invention. Moreover, Gruber *et al.* note that the 250 µg/kg/hr dose of rAPC infusion did not prevent the increase in circulating markers of platelet activation (see 2nd paragraph, right column, p. 581), and that infusion of 0.25 µg/kg/hr had no effect on the in vitro, t-PA dependent fibrinolysis assay (see 2nd paragraph, right column, p. 582). Thus, Gruber *et al.* teaches a preferable dose of 1000 µg/kg/hr, which is 20-fold higher than the highest dose of the present invention.

In addition, Gruber *et al.* administer aPC by bolus injection of 1/3 of the dose followed by continuous infusion of the remainder of the dose for 1 hour. In contrast, the present invention provides for administration by continuous infusion over a period of 1-240 hours, or alternatively, administration by a bolus injection of 1/3 of the dose per hour followed by continuous infusion of the remainder of the dose for 23 hours, to achieve the appropriate dose administered over 24 hours total. Gruber *et al.* obtained plasma levels of 340 to 490 ng/mL at the lower dose taught therein and 1,900 to 2000 ng/mL at the preferable, higher dose taught therein. In contrast, the present invention achieves an aPC plasma level of about 2 ng/ml to about 300 ng/ml. Gruber *et al.* therefore has three deficiencies with respect to the present invention in that it teaches a high dose level which would subject patients to a high risk of bleeding complications, it fails to teach continuous infusion and its duration, and it teaches a combination of bolus/continuous infusion which differs significantly from that of the present invention and which would subject a patient to adverse effects due to overly high levels of aPC. Gruber *et al.* therefore does not teach the limitations of the claims, nor does Gruber *et al.* suggest an expectation that the lower dose claims of the present invention would be successful therapy.

In view of the above, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness since there is not suggestion or motivation for one of skill in the art to combine Glas-Greenwalt *et al.* with Gruber *et al.* and Foster *et al.*; one of skill in the art would not have a reasonable expectation of success of the present invention over these references; and Gruber *et al.* does not teach or suggest all the limitations of the claims of the present invention. Accordingly, Applicants request withdrawal of the rejection of claims 21, 22, and 25-28 under 35 U.S.C. § 103(a) and further submit that newly added claim 37 is nonobvious over the prior art.

Rejection of Claims 29-36 under 35 U.S.C. § 103(a)

Claims 29-36 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Glas-Greenwalt *et al.*, Gruber *et al.*, and Foster *et al.* in further view of Hollenbeck *et al.*, Nephrol. Dial. Transplant. (1198) 13:76-81 (Hollenbeck *et al.*). Applicants respectfully traverse this rejection as applied to amended claims 29, 30, and 33-36. The Examiner has concluded it would have been obvious to one of ordinary skill in the art to develop a method of treatment for HUS using recombinant human PC in view of the teachings of Glas-Greenwalt *et al.*, Gruber *et al.*, and Foster *et al.* (discussed above) combined with Hollenbeck *et al.*'s characterization of TTP and HUS as similar and that prognosis of HUS is favorably influenced by plasma exchange. Applicants respectfully assert that the Examiner has failed to set forth a *prima facie* case of obviousness and request withdrawal of this rejection.

Hollenbeck *et al.* teach that TTP and HUS are characterized by similar outcomes, and that the overlap between the two clinical pictures is such that the two disorders are increasingly referred to as HUS-TTP. While Hollenbeck *et al.* teach that plasma exchange provides therapeutic value toward maintaining renal function in HUS-TTP patients, Hollenbeck does not make mention of any of the factors addressed by Glas-Greenwalt *et al.*, let alone protein C. Conversely, Glas-Greenwalt *et al.* does not discuss HUS, the development of end-stage renal disease, and the factors examined by Hollenbeck *et al.* Thus the references themselves provide no motivation to combine Hollenbeck *et al.* with Glas-Greenwalt *et al.* While one of skill in the art likely would have knowledge of Hollenbeck *et al.* and Glas-Greenwalt *et al.*, one of skill would not be motivated to combine Hollenbeck *et al.* and Glas-Greenwalt *et al.* with Gruber *et al.* and Foster *et al.* for the reasons described above in respect of lack of motivation to combine Glas-Greenwalt *et al.* with Gruber *et al.* and Foster *et al.*

The Examiner states that it is well known in the art that plasma exchange, as used by Hollenbeck *et al.*, is a source of protein C and aPC. Combining Hollenbeck *et al.* with Glas-Greenwalt *et al.*, one could at most infer that levels of protein C might be compromised in HUS, since 1/3 of the TTP patients examined by Glas-Greenwalt *et al.* had normal levels of protein C. For reasons discussed above regarding differences in protein C and aPC and the lack of a reasonable expectation of success

upon combination of Glas-Greenwalt *et al.*, Gruber *et al.*, and Foster *et al.*, combination of Hollenbeck *et al.* with Glas-Greenwalt *et al.*, Gruber *et al.*, and Foster *et al.* fails to provide a reasonable expectation of success.

In particular, as noted above, Gruber *et al.* teaches beneficial use of aPC in the prevention of thrombin formation due to its anti-coagulant properties. At the time of the present invention, plasma infusion and exchange were known to successfully treat HUS, but the mechanism had not been defined (see last paragraph of left column and first two paragraphs of right column of page S48, Neild, Kidney International (1998) 53, S45-49, ref. CA of IDS filed 6/24/03 (Neild)). Moreover, anticoagulants had not been shown to be of benefit (see third paragraph, right column, page S48, Neild). Thus, one of skill in the art would not have had a reasonable expectation of success in treating HUS by combining Hollenbeck *et al.* and Gruber *et al.* Moreover, the deficiency of this combination is not remedied in view of Foster *et al.*, for reasons discussed above with respect to combination of Glas-Greenwalt *et al.*, Gruber *et al.*, and Foster *et al.*

Finally, combination of Hollenbeck *et al.* with Glas-Greenwalt *et al.*, Gruber *et al.*, and Foster *et al.* fails to provide all the limitations of the claims. The Examiner states it would have been well within the skill of the art to empirically set up dosages and safe methods of infusion for treatment of HUS in view of the treatment disclosed in Gruber *et al.* As noted above, Gruber *et al.* has three deficiencies with respect to the present invention in that it teaches a high dose level which would subject patients to a high risk of bleeding complications, it fails to teach continuous infusion and its duration, and it teaches a combination of bolus/continuous infusion which differs significantly from that of the present invention and which would subject a patient to adverse effects due to overly high levels of aPC. Applicants have discovered a critical dosage range and a critical duration and mode of continuous infusion, since higher dosages create risks of bleeding which could cause serious adverse events or lethality in humans. Furthermore, Gruber *et al.* does not provide an expectation that the lower doses of the present invention would provide successful therapy, as discussed above.

In view of the above, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness since there is no suggestion or motivation for one of skill in the art to combine Hollenbeck *et al.* with Glas-

Greenwalt *et al.*, Gruber *et al.* and Foster *et al.*; one of skill in the art would not have a reasonable expectation of success of the present invention over these references; and Gruber *et al.* does not teach or suggest all the limitations of the claims of the present invention. Accordingly, Applicants request withdrawal of claims 29, 30, and 33-36 under 35 U.S.C. § 103(a) and further submit that newly added claim 38 is nonobvious over the prior art

Conclusion

Having addressed all outstanding issues, Applicants respectfully request entry and consideration of the foregoing amendments which place the application in condition for allowance. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is invited to telephone the undersigned at the number below.

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March 17 2005